Claim Rejections - 35 USC § 103(a)

3-4. Claims **1-32** stand rejected under 35 U.S.C. 103(a) as being unpatentable over **[DAIFOTIS, ET AL. (WO 9904773, PTO-892) in view of Lichtenberger et al.(PTO-1449 submitted October 12, 2001.)**. Applicant respectfully traverses this rejection.

Daifotis et al. disclose that bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate, within the instant claims, are known to be useful in pharmaceutical compositions and methods for treating osteoporosis. See abstract, page 1 lines 14-15 and page 2 lines 1-15. Daifotis et al. also disclose that bisphosphonates are known to have low bioavailability from GI tract and therefore cause adverse GI effects. See abstract, page 1-3. Further, Daifotis et al. disclose methods therein for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the adverse GI effects. See abstract and page 7.

Daifotis et al. do not expressly disclose the employment of at least one bisphosphonate in combination with one zwitterionic phospholipid in a pharmaceutical composition. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered.

Lichtenberger et al. disclose that zwitterionic phospholipids (within the instant claims) are capable of reducing GI irritating (adverse) effects and is therefore useful in combining with NSAID drugs in pharmaceutical compositions since NSAID drugs may cause GI adverse effects, e.g., inducing GI ulcers and bleeding. See abstract and col.1- 2, and col.1 0 lines 50-61. Lichtenberger et al. also disclose the effective amounts of zwitterionic phospholipids in the pharmaceutical compositions therein. See col.12 lines 12-34.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ one zwitterionic phospholipid in combination with a bisphosphonate in a pharmaceutical composition, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ one zwitterionic phospholipid in combination with a bisphosphonate in a pharmaceutical composition since zwitterionic phospholipids are known to be capable of reducing GI irritating (adverse) effects that caused by other drugs such as NSAIDs according to Lichtenberger et al. Moreover, bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate are known to cause adverse GI effects and the purpose of the method of Daifotis et al. is known to minimize the adverse GI effects induced by bisphosphonates. Therefore, one of ordinary skill in the art would have reasonably expected that combining one

zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate. Hence, the combined teachings of Daifotis and Lichtenberger has provided the motivation of the instant invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts or ratio of zwitterionic phospholipid and a bisphosphonate in a composition because the effective amounts of zwitterionic phospholipid to be administered are known in the art. Moreover, the optimization of amounts of active agents to be administered is considered well within the skill of artisan, involving merely routine skill in the art.

Applicant agrees that Daifotis et al. disclose bisphosphonates and that bisphosphonates can cause adverse GI effects when ingested. Applicant also agrees that Lichtenberger et al. disclose that zwitterionic phospholipids when combined with NSAIDS reduce the GI toxic effects of NSAIDs when ingested. However, Applicant disagrees that these two references are properly combinable and that their combination renders the present invention obvious.

The Examiner contends that these references are properly combinable for the purposes of an obviousness determination. Applicant disagrees. The references simply establish that the elements of the claimed invention are known, but there is no motivation to combine because there is no reasonable expectation that their combination would be successful. "[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness." *In re Longi,* 759 F.2d 887, 896, 225 USPQ 645, 651-52 (Fed. Cir. 1985). "It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997). This showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not "evidence." *See Dembiczak*, 175 F.3d at 1000, 50 USPQ2d at 1617. However, the suggestion to combine need not be express and "may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). Although the suggestion to combine references may flow from the nature of the problem, *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75

F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996), "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness," *Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh*, 139 F.3d 877, 880, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998). Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, `the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting *Lindemann*, 730 F.2d at 1462, 221 USPQ at 488).

A major problem with pharmaceuticals, and chemicals in general, is that the effects of their combination is generally unpredictable, especially, when the compared compounds have little in common. It is well known that even minor changes to a composition or formulation can result in inactivity, a complete change in mode of activity, a change in the efficacy in unpredictable ways, a change in bio-availability in unpredictable ways, *etc.* and, in certain extreme cases, lead to extremely dangerous consequences, e.g., thalidamide.

Moreover, the combination is even more problematic in this situation. NSAIDs and zwitterionic phospholipids are fundamentally different chemical compositions. While bisphosphonates are more similar to the zwitterionic phospholipids than to the NSAIDs. Thus, one could draw the conclusion that a phospholipid would have no effect on a similar type of molecular species. If an ordinary artisan could come to the conclusion that the effect of combining these two classes of compounds is simply unpredictable, then that conclusion argues strongly against obviousness.

Moreover, Applicant believes the motivation to combine these to references is derived exclusively from hindsight, a view of the world that is impermissible in the examination of inventions for obvious. "Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). As the Examiner is well aware, an invention is always obvious after the fact. It is before the fact that the obviousness determination must be made. Without the knowledge that the present composition actually works, an ordinary artisan

simply did not have enough information to determine one way or the other that the combination would be beneficial.

Furthermore, Applicant believes that Daifotis et al. actually teaches away from any motivation to reduce GI toxicity because Daifotis et al. tells that would that they have solved the problem of GI toxicity by using a "continuous schedule" having a selected dosing interval. Thus, to an ordinary artisan, Daifotis et al. has solved the problem that would act to motivate an ordinary artisan to seek out a method to reduce the GI toxicity of bisphosphonates. The Examiner even admits this: "the purpose of the method of Daifotis et al. is known to minimize the adverse GI effects induced by bisphosphonate."

In summary, the combination of the references is improper for at least the following reasons: 1) impressible use of hindsight, 2) no suggestion or motivation to combine because there is no similarity between NSAID and bisphosphonates, and 3) Daifotis et al. solved the problem of adverse GI effects induced by bisphosphonates, which would dissuade an ordinary artisan from solving a problem that had already been solved. Applicant, therefore, respectfully requests withdrawal of this 103(a) rejection and allowance of the case.

If it would be of assistance in resolving any issues in this application, the Examiner is kindly invited to contact applicant's attorney Robert W. Strozier at 713.977.7000

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Respectfully submitted,

Robert W. Strozier
Reg. No. 34,024